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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,142	MILLER	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-35,39-43 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35,39-43 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 33-35, 39-43 and 47-49 are pending.

2. The references C133, C134 and C139 on PTO 1449 filed 3/28/05 have not been considered and have been crossed out because the date of the poster presentation for references are not disclosed.

3. In view of the amendment filed 2/11/05, the following rejections remain.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 33-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 6,270,749 B1 (filed June 10, 1999; PTO 892) in view of Adamis et al (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892).

The '749 patent teaches a method of treating unwanted choroidal neovasculature such as aged related macular degeneration (See abstract, col. 6, lines 25-42, col. 23, lines 10-11, in particular) comprising endothelial cells in the eyes of a mammal such as New Zealand White rabbits (see col. 23, line 23, in particular) or subject such as human which is also a primate by

administering to the mammal an effective amount of an anti-angiogenic factor such as monoclonal antibody to VEGF (See col. 10, lines 48-50, col. 19, lines 30-45, in particular) conjugated to a tetrapyrrole derivative photosensitizer such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives (See col. 2, lines 65-70, in particular) and irradiating the choroidal neovasculature with laser light (see col. 21, lines 5-8, in particular) such that the light is occlude the choroidal neovasculature (See col. 25, line 31, in particular). The advantage of the reference method is that the PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular).

The invention in claims 33, and 41, differs from the teachings of the reference only in that the method wherein the antibody that binds preferentially to VEGF and is not coupled to lutetium texaphyrin.

Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (see abstract, in particular).

The '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular), or targeted immunotoxins or coaguligands (See col. 123, lines 9-10, Paragraph 461, in particular). The '219 patent teaches the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a mammal an unconjugated lutetium texaphyrin for a method of unwanted choroidal neovasculature in a mammal as taught by the '749 patent in combination with the anti-VEGF as taught by Adamis et al or the'219 patent or the angiostatin as taught by the '219 patent before administering photosensitizer as taught by the '219. It has been well established in the art that anti-VEGF conjugated lutetium texaphyrin is from unconjugated or uncoupled anti-VEGF to lutetium texaphyrin and there is no evidence that the method of use described in the instant claims would differ in an unexpected manner from those described in the

reference. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because the '749 patent teaches tetrapyrrole derivative photosensitizer such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives is effective for treating unwanted neovascularization and PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular). Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular). The '219 patent teaches anti-VEGF antibody in combination with other therapeutic agent is effective for inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) and angiostatin inhibits angiogenesis (See col. 120, line 59, Table D, in particular). The '219 patent further teaches that the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone. The recitation of anti-angiogenesis factor and the tetrapyrrole derivative photosensitizer are not coupled to one another is an obvious variation of the reference teachings because the VEGF monoclonal antibody and photosensitizer in the conjugated anti-VEGF to photosensitizer taught by the '749 patent before conjugation are not coupled to each other. Further, The '219 patent teaches combination of angiostatin or anti-VEGF in combination with chemotherapeutic or radiotherapeutic for a method of treating unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular).

Applicants' arguments filed 2/11/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) the anti-angiogenesis factor and the photosensitizer are not coupled or conjugated to one another because the photosensitizer is administered after the anti-angiogenesis factor. The '749 patent merely discusses these molecules in the context of targeting

and nowhere suggests administering an anti-VEGF antibody to the recipient to reduce or inhibit the formation of new blood vessels in the recipient. Applicants submit that the skilled artisan would not have been motivated to administer the targeting moiety and photosensitizer as unconjugated entities as this would effectively undermine the purpose of benefit of having a targeting moiety. In effect, the '749 patent teaches away from the claimed invention of using a photosensitizer not coupled or conjugated to the anti-angiogenesis factor. Applicants submit that the secondary references (i.e., Adamis and the '219 patent) fail to make up for the deficiencies in the '749 patent. (2) Adamis describes the use of an anti-VEGF monoclonal antibody to prevent iris neovascularization following retinal ischemia in non-human primates. Adamis, however, fails to teach or suggest combining an anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature. Furthermore, Applicants submit that Adamis teaches the treatment of iris not choroidal neovascularization of the eye, as required by the claimed invention. (3) The '219 patent describes the use of anti-VEGF antibodies that inhibit VEGF binding to a VEGF receptor, and the use of such antibodies for the treatment of choroidal neovascularization. The 4219 patent, however, fails to teach or suggest combining the anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature. (4) Contrary to the Examiner's assertion that "there is no evidence that the method of use described in the instant claims would differ in an unexpected manner from those described in the references" Applicants disclose in their specification that angiostatin and Lu--Tex showed a synergistic cytotoxic effect on BRCE endothelial cells (see, page 25, first paragraph, lines 7-10). The effect of this combination exceeded the cytotoxicity of either treatment alone, and also exceeded the arithmetic sums of their respective toxicities. The surprising effectiveness of this combination could not have been predicted by the skilled artisan based on teachings present in any of the references replied upon by the Examiner in the outstanding Action. (5) The claimed combination is also effective in vivo for the treatment of choroidal neovascularization as evidenced in an abstract (made of record as citation C115), which was presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida. The abstract describes experiments that were carried out using methods taught in Applicants' specification (e.g., pages 3-4, page 8, paragraph 3, and pages 13-17). These experiments showed that under the conditions tested, the administration of angiostatin on its own did not prevent the growth of choroidal neovascular membranes. In contrast, the combination of angiostatin and PDT significantly increased the number of lesions without angiographic leakage.

For example, 42.9% of the lesions tested lacked angiogenic leakage when treated only with PDT (photodynamic therapy) at 10J/cm^2. In contrast 90-100% of the lesions tested lacked angiogenic leakage when treated with PDT when combined with angiostatin.

In response to applicants' argument that claim 33 has been amended to recite the anti-angiogenesis factor and the tetrapyrrole derivative photosensitizer are not coupled to one another, the recitation of anti-angiogenesis factor and the tetrapyrrole derivative photosensitizer are not coupled to one another is an obvious variation of the reference teachings because prior to conjugation, the VEGF monoclonal antibody and photosensitizer in the conjugate taught by the '749 patent are not coupled to each other. Further, the '219 patent teaches unconjugated angiostatin or anti-VEGF in combination with chemotherapeutic or radiotherapeutic for a method of treating unwanted choroidal neovasculature such as such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular). The combinations taught by '219 patent are not conjugated.

In response to applicants' argument that Adamis teaches the treatment of iris not choroidal neovasculalization of the eye, as required by the claimed invention, the '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular). The concept of inhibiting neovascularization using anti-VEGF antibody or PDT is universal regardless whether it is the iris as taught by Adamis or the choroidal neovasculalization of the eye as taught by the '219 patent or the '749 patent.

In response to applicants' argument that Adamis and the '219 patent fail to teach or suggest combining an anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature, the '749 patent teaches a method of treating unwanted choroidal neovasculature such as aged related macular degeneration (See abstract, col. 6, lines 25-42, col. 23, lines 10-11, in particular) comprising endothelial cells in the eyes of a mammal such as New Zealand White rabbits (see col. 23, line 23, in particular) or a subject such as human, which is also a primate, by administering to the mammal an effective amount of an anti-angiogenic factor such as monoclonal antibody to VEGF (See col. 10, lines 48-50, col. 19, lines

30-45, in particular) conjugated to a tetrapyrrole derivative photosensitizer such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives (See col. 2, lines 65-70, in particular) and irradiating the choroidal neovasculature with laser light (see col. 21, lines 5-8, in particular) such that the light is occlude the choroidal neovasculature (See col. 25, line 31, in particular).

In response to applicants' argument that the specification on page 25, first paragraph, lines 7-10 discloses that angiostatin and Lu-Tex showed a synergistic cytotoxic effect on BRCE endothelial cells, and that the effect of this combination exceeded the cytotoxicity of either treatment alone, and also exceeded the arithmetic sums of their respective toxicities, it is noted that the experiment described on page 25 was done *in vitro*, not *in vivo*. The claims recite a method of treating unwanted choroidal neovasculature comprising *administering to a mammal* an anti-angiogenesis factor such as an angiostatin or VEGF antibody and photosensitizer such as leutium or benzoporphyrin derivative wherein the anti-angiogenesis factor and the photosensitizer are not coupled to one another. The specification on page 26 merely discloses treating BRCE cells in vitro with angiostatin before Lu-Tex/PDT at a light dose or fluence of 20 J/cm^2 induces nearly 100% apoptosis. In the absence of angiostatin, a light dose of 40 J/cm^2 is required to achieve this level of toxicity. The specification on page 25 discloses that angiostatin was not effective in potentiating the effect of Lu-Tex/PDT if delivered after PDT. Further, there is a lack of in vivo data for VEGF antibody and Lu-Tex/PDT. Finally, there is a lack of unexpected results for the claimed method comparing the angiostatin or VEGF antibody conjugated Lu-Tex/photosensitizer.

In response to applicants' argument that in vivo treatment of choroidal neovascularization is evidenced in an abstract (made of record as citation C115), which was presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida, it is suggested that applicants resubmit said abstract in the form of a declaration. Although the abstract C115 was cited on PTO 1449 filed 4/23/03, the actual abstract is missing from the electronic imaged file.

7. Claims 33-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of US Pat No 5,733,876 (March 1998, PTO 892) and Adamis *et al* (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892).

The teachings of Kramer *et al* have been discussed supra.

The claimed invention differs from the combined teachings of the references only in that the anti-angiogenic factor is angiostatin instead of anti-VEGF antibody.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (see abstract, in particular).

The '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular), or targeted immunotoxins or coaguligands (See col. 123, lines 9-10, Paragraph 461, in particular). The '219 patent teaches the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-VEGF antibody in the method of treating unwanted choroidal neovasculature as taught by Adamis *et al* and the '219 patent for the angiopoietin as taught by the '876 patent by administering the angiopoietin before any conventional therapy as taught by the '219 patent, follows by administering the benzoporphyrin derivative verteporfin liposome that is effective for treatment of choroidal neovascularization as taught by Kramer *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because angiostatin may be used in combination with other composition to inhibit angiogenesis or growth of endothelial cells associated with macular degeneration as taught by the '876 patent. Kramer *et al* teach benzoporphyrin derivative verteporfin liposome is

effective for treatment of choroidal neovascularization with minimal retinal and choroidal damage and no major local adverse effects (See abstract, in particular). Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits neovascularization (see abstract, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease (macular degeneration) would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

Applicants' arguments filed 2/11/05 have been fully considered but are not found persuasive.

Applicants' position is that Kramer, describes the use of liposomal benzoporphyrin derivative (BPD) verteporfin photodynamic therapy for the treatment of choroidal neovascularization in monkeys. Kramer, however, fails to teach or suggest the additional step of combining an anti-angiogenesis factor during photodynamic therapy. Adamis describes the use of an anti-VEGF monoclonal antibody to prevent iris neovascularization following retinal ischemia in non-human primates. Adamis fails to teach or suggest combining the anti-VEGF monoclonal antibody with photodynamic therapy. The '219 patent describes the use of anti-VEGF antibodies that inhibit VEGF binding to a VEGF receptor, and the use of such antibodies for the treatment of choroidal neovascularization. Applicants submit, however, that the '219 patent fails to teach or suggest combining the anti-VEGF antibody with photodynamic therapy. There is nothing in any of the applied references that would motivate the skilled artisan to combine their respective teachings to arrive at a method where an anti-angiogenesis factor is combined with a photodynamic therapy-based method for treating unwanted choroidal neovascularization. For the sake of argument only, even if the teachings of Kramer, Adamis, the '219 patent and the '876 patent were combined in the manner suggested in the Office Action, Applicants submit that their combined teachings fail to teach or suggest the claimed subject matter taken as a whole. For example, Applicants submit that the applied references fail to teach or suggest a method where occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as is required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of

photodynamic therapy and administration of and anti-angiogenic factor, i.e., steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c), as is required by claim 41. The synergistic properties of the claimed invention were discussed previously and are again reiterated here. Applicants submit that teachings of the applied reference, either alone or in combination, fail to teach the claimed subject matter, taken as a whole, and Applicants respectfully request that this rejection of clams 33 and 41, and the claims depending therefrom, be reconsidered and withdrawn.

In response to Applicants' arguments that Kramer fails to teach or suggest the additional step of combining an anti-angiogenesis factor during photodynamic therapy, one cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In response to applicants' argument that Adamis teaches the treatment of iris not choroidal neovasculalization of the eye, as required by the claimed invention, the '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular). The '749 patent also teaches a method of treating unwanted choroidal neovasculature by administering anti-VEGF antibody (see col. 10, lines 48-50, col. 19, lines 30-45, in particular).

In response to applicants' argument that Adamis and the '219 patent fail to teach or suggest combining an anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for treating choroidal neovasculalization. The teachings of Adamis, the '219 patent and Kramer et al have been discussed supra and are incorporated here by reference.

In contrast to applicants' argument that the applied references would not motivate the skilled artisan to combine their respective teachings to arrive at a method, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. The combined teachings particularly primary reference Kramer *et al*

provide clear direction, motivation and expectation of success in treating disease such as unwanted choroidal neovasculature with benzoporphyrin derivative such as verteporfin liposome. The secondary reference '876 patent also provides direction, motivation and expectation of success in treating macular degeneration associated with unwanted choroidal neovasculature with angiostatin (see column 9, line 66 bridging column 10, line 9-10 claims 1-13 of '876, abstract, in particular). The '219 patent also provides clear direction, motivation and expectation of success in treating disease such as unwanted choroidal neovasculature with VEGF antibody or angiostatin in combination with conventional chemotherapeutic, radiotherapeutic (See col. 120, line 59, Table D, in particular). The strongest rationale for combining references is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), see MPEP 2144.

In response to Applicants' argument that the combined teachings of the references fail to teach or suggest the synergistic effect of photodynamic therapy and anti-angiogenesis factor such as angiopoietin and VEGF antibody, the expectation that the prior art elements PDT in combination with anti-VEGF antibody or angiopoietin will perform their expected functions to achieve their expected results when combine for their common known purpose such as treating unwanted choroidal neovasculature. Section MPEP 2144.07. The synergistic effect of the combined elements is expected by one ordinary skill in the art given that the claimed method treats the same population, the same the disease such as unwanted choroidal neovasculature and using the same products photosensitizer and angiostatin or anti-VEGF as taught by the cited prior arts.

8. Claims 33-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of US Pat No 6,270,749 B1 (of record, Aug 2001, PTO 892) and Adamis *et al* (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892).

The teachings of Kramer *et al* have been discussed supra.

The claimed invention differs from the combined teachings of the references only in that the method of treating unwanted choroidal neovasculature wherein the tetrapyrrole derivative is lutetium texaphyrin instead of bezoporphyrin derivative Verteporfin.

The '749 patent teaches the use of photosensitizer such as texaphyrin complex with a diamagnetic metal such as Lutetium which is a tetrapyrrode derivative (See Abstract, column 8, lines 5-17, in particular) for a method of treating age-related macular degeneration (See column 23, lines 6-11, in particular). The '749 patent teaches the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular).

Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (see abstract, in particular).

The '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular), or targeted immunotoxins or coaguligands (See col. 123, lines 9-10, Paragraph 461, in particular). The '219 patent teaches the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the bezoporphyrin derivative Verteporfin in the method of treating choroidal neovascularization as taught by Kremer et al for the lutetium texaphyrin as taught by the '749 for a method of treating unwanted choroidal neovasculature in a mammal as taught by Kramer *et al,* Adamis *et al* the '219 patent and the '749 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '749 patent teaches photosensitizer such as Lutetium texaphyrin is effective for treating unwanted choroidal neovasculature associated with age-related macular degeneration because the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile

in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

Applicants' arguments filed 2/11/05 have been fully considered but are not found persuasive.

Applicants' position is that the applied references fail to teach or suggest a method where occlusion caused by administering an anti-angiogenic factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as is required by claim 33. Similarly, Applicants submit that their combined teaching fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of photodynamic therapy and administration of and anti-angiogenic factor, i.e., steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c), as is required by claim 41. The synergistic properties of the claimed invention were discussed previously and are again reiterated here. Applicants submit that teachings of the applied reference, either alone or in combination, fail to teach the claimed subject matter, taken as a whole, and Applicants respectfully request that this rejection of clams 33 and 41, and the claims depending therefrom, be reconsidered and withdrawn.

In response to Applicants' argument that the combined teachings of the references fail to teach or suggest the synergistic effect of photodynamic therapy and anti-angiogenesis factor such as angiopoietin and VEGF antibody, the expectation that the prior art elements PDT in combination with anti-VEGF antibody or angiopoietin will perform their expected functions to achieve their expected results when combine for their common known purpose such as treating unwanted choroidal neovasculature. Section MPEP 2144.07. The synergistic effect of the combined elements is expected by one ordinary skill in the art given that the claimed method treats the same population, the same the disease such as unwanted choroidal neovasculature and

using the same products photosensitizer and angiostatin or anti-VEGF as taught by the cited prior arts.

In response to Applicants' arguments that Kramer fails to teach or suggest the additional step of combining an anti-angiogenesis factor during photodynamic therapy, one cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In response to applicants' argument that Adamis teaches the treatment of iris not choroidal neovasculalization of the eye, as required by the claimed invention, the '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody (not coupled to) such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular). The '749 patent also teaches a method of treating unwanted choroidal neovasculature by administering anti-VEGF antibody (see col. 10, lines 48-50, col. 19, lines 30-45, in particular).

In response to applicants' argument that Adamis and the '219 patent fail to teach or suggest combining an anti-VEGF antibody with a photodynamic therapy-based treatment of unwanted choroidal neovasculature, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for treating choroidal neovasculalization. The teachings of Adamis, the '219 patent and Kramer et al have been discussed supra and are incorporated here by reference.

In contrast to applicants' argument that the applied references would not motivate the skilled artisan to combine their respective teachings to arrive at a method, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. The combined teachings particularly primary reference Kramer *et al* provide clear direction, motivation and expectation of success in treating disease such as unwanted choroidal neovasculature with benzoporphyrin derivative such as verteporfin liposome. The secondary reference '876 patent also provides direction, motivation and expectation of success in treating macular degeneration associated with unwanted choroidal neovasculature with angiostatin (see column 9, line 66 bridging column 10, line 9-10 claims 1-13 of '876, abstract, in

particular). The '219 patent also provides clear direction, motivation and expectation of success in treating disease such as unwanted choroidal neovasculature with VEGF antibody or angiostatin in combination with conventional chemotherapeutic, radiotherapeutic (See col. 120, line 59, Table D, in particular). The strongest rationale for combining references is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), see MPEP 2144.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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